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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/091,300	03/04/2002	Patricia Rockwell	11245/46211	1694

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/091,300	ROCKWELL ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-18 and 21-67* is/are pending in the application.

4a) Of the above claim(s) *6,10,15,18,22,27,29-61 and 63-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9,11-14,16-17,21,23-26,28,62 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/9/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 7-8 and 19-20 have been canceled.

Claims 1, 5, 9, 17, 21 and 62 have been amended.

Claims 6, 10, 15, 18, 22, 27, 29-61 and 63-66 remain withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

2. Claims 1-5, 9, 11-14, 16-17, 21, 23-26, 28, 62 and 67 are under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. Claims 1, 5, 7-8, 11-14, 17, 19-21, 23-26, 28, 62 and 67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 15, 17, 25-26 and 32 of copending Application No. 09/798,689 in view of Queen et al is withdrawn in view of the amendments to the claims and Applicant's arguments filed 2/1/2005.

New Grounds of Rejections

6. Claims 11-14 and 23-26 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-14 and 23-26 recite the limitation "the antibody". There is insufficient antecedent basis for this limitation in the claim. Claims 11-14 and 23-26 are dependent

upon base claim 1, which recites two antibodies and it is unclear which of these two antibodies are being referred to in claims 11-14 and 23-26. Are both VEGFR and EGFR antibodies human, chimeric and humanized?

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The response filed 1/3/2005 has introduced NEW MATTER into the claims. Claim 21 as amended now recites wherein the EGFR antibody inhibits binding of EGFR to ATP. The response filed 1/3/2005 did not point out where support for amended claim 21 could be found in the disclosure as-filed. Although the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims, when filing an amendment an applicant should show support in the original disclosure for new or amended claims. See MPEP 714.02 and 2163.06 ("Applicant should therefore specifically point out the support for any amendments made to the disclosure."). Claim

21 as originally filed recited the limitation "wherein the EGFR antagonist inhibits binding of EGFR to ATP." There is insufficient written support for the presently claimed narrower limitation that the anti-EGFR antibody inhibits binding of EGFR to ATP. Claim 21 now recites limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in amended claim 21, which did not appear in the specification, as-filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in present claim 21 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

Priority

9. The instant claims are directed to anti-VEGFR and anti-EGFR antibodies in a method of inhibiting tumor growth in humans. Written support for the instantly claimed method can be found in the parent application (USSN 09/798,689), however, the grandparent application (USSN 09/401,163) does not have adequate written support for tumor inhibition methods comprising administering antibodies that bind to VEGFR and EGFR. Thus, the instant claims are granted the priority date of USSN 09/798,689, i.e., 3/2/2001.

If applicant desires priority prior to 3/2/2001, applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1, 2, 9, 11-14, 23-26, 28, 62 and 67 are rejected under 35 U.S.C 102(e) as anticipated by Zhu (US 2004/0259156 A1, 5/24/2000).

The claims are drawn to a method of inhibiting tumor growth comprising administering to a human a anti-vascular endothelial growth factor receptor (VEGFR) antibody and an anti-epidermal growth factor receptor (EGFR) antibody wherein the antibodies are chimeric, humanized or human antibodies and the administration further comprises a chemotherapeutic agent or radiation and kits comprising such. Applicant is reminded that the intended use of a product claim (i.e., kit) carries no patentable weight [MPEP 2111.02]. Thus, the intended use of the kit for inhibiting tumor growth is given no patentable weight. For this rejection the claims are interpreted as being drawn to a bispecific antibody that binds both VEGFR and EGFR.

Zhu teaches a method of inhibiting or reducing tumor growth comprising administering an antigen-binding protein, wherein the antigen-binding protein is bispecific and binds the VEGF receptor Flt-1 and the EGFR and blocks ligand binding to

neutralize receptor activation (see page 2, paragraph [0020] and page 7, paragraph [0064]). Zhu teach that chimeric, human and humanized antibodies (i.e., antigen-binding proteins) (see pages 8-9 and page 2, paragraph [0016]) and Zhu teaches chemotherapeutic agents and radioisotopes conjugated to the antigen-binding protein, and hence, the method further comprises administering a chemotherapeutic agent or radiation.

Although claims 62 and 67 recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy.

Therefore, Zhu anticipates the claims.

12. Claims 1-5, 9, 11-14, 16-17, 23-26, 28, 62 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rockwell et al (Molecular and Cellular Differentiation. 3(4): 315-335, 1995, Ids filed 6/18/2003) in view of Ciardiello et al (Clinical Cancer Research, 6:3739-3747, September 2000) and Siemeister et al (Cancer and Metastasis Reviews 17: 241-248, 1998, cited previously) and Queen et al (U.S. Patent No. 5,530,101, filed 12/19/1990, cited previously).

The claims are drawn to a method of inhibiting tumor growth comprising administering to a human a anti-VEGFR antibody and an anti-EGFR antibody wherein the antibodies are chimeric, humanized or human antibodies and the administration further comprises a chemotherapeutic agent or radiation and kits comprising such.

Applicant is reminded that the intended use of a product claim (i.e., kit) carries no patentable weight [MPEP 2111.02]. Thus, the intended use of the kit for inhibiting tumor growth is given no patentable weight.

Rockwell et al teach that treatment of cancer with neutralizing monoclonal antibodies that block the activation of essential PTK receptors offers a promising strategy for suppressing tumor growth and tumor angiogenesis and Rockwell teaches that overexpression of EGFR correlates with poor prognosis for many cancers, including breast, prostate, non-small cell lung carcinoma, bladder, head and neck, and ovarian carcinomas (see page 317) and high levels of VEGF expression occurs in various human tumors including colorectal cancer-induced metastasis (see page 322). Rockwell et al teaches that monoclonal antibodies 225 and C225 (chimeric version of 225) that bind EGFR and inhibit ligand binding and the 225 antibody inhibits the growth of A431 (human epidermoid carcinoma) xenografts in nude mice when given within 5 days of tumor inoculation (see page 317). Rockwell et al also teach a VEGFR-specific monoclonal antibody, DC101, which blocked VEGF receptor activation in the A431 tumor cell line (see page 322 and Figure 4A and 4B) and DC101 significantly inhibited the growth of new and established tumors (see page 323). Rockwell et al teach that DC101 is cross-reactive with human VEGFR receptor forms (i.e., flt-1 and KDR) and thus, has the potential to inhibit VEGF-mediated activation of receptors on endothelial cells induced to proliferate and form blood vessels during tumor angiogenesis (see page 323). Finally, Rockwell et al acknowledges "there is mounting preclinical and clinical data that combination therapies may be more efficacious than single agent use" (see

page 327). Rockwell et al do not specifically teach combining an anti-VEGFR antibody and an anti-EGFR antibody for inhibiting tumor growth or humanized or chimeric VEGFR antibodies or intravenous administration or a kit comprising the anti-VEGFR antibody and the anti-EGFR antibody. These deficiencies are made up for in the teachings of Ciardiello et al and Siemeister et al and Queen et al.

Ciardiello et al teach that treatment of colon cancer xenografts in mice with a VEGF antisense oligonucleotide or treatment with monoclonal antibody C225 (chimeric human-mouse IgG1) results in a mostly cytostatic and reversible growth-inhibitory effect, whereas when the two agents are used in combination, an almost complete suppression of tumor growth in all mice was observed (see page 3743, Table 2, Figures 5-7). Ciardiello et al teach that VEGF is a potent angiogenic factor and specific mitogen for endothelial cells, activates the angiogenic switch in vivo, and enhances vascular permeability and enhanced expression of VEGF has been observed in human cancer cell lines and in cancer patients with different malignancies including colorectal, breast, non-small cell lung, and ovarian cancers and VEGF is directly correlated with increased neovascularization as measured by microvessel count within the tumor (see page 3740).

Siemeister et al teach that VEGFR receptors (flt-1 and KDR/flk-1) are up-regulated "when angiogenesis takes place, as in the case of tumor growth" (see page 243, right column). Siemeister et al teach that "the growth of malignant tumors is associated with tissue hypoxia and hypoxia has been described to be a major mechanism leading to the up-regulation of VEGF and its receptors in vivo" (see page

244). Siemeister et al teach that decreased VEGF expression in tumor cells has been achieved by blocking EGF-stimulated expression of VEGF in A431 tumor cells using an anti-EGFR neutralizing antibody (see page 245)

Queen et al teach chimeric, human and humanized antibodies for human therapy (see entire document, particularly column 11, lines 53-65, columns 2-3, 12-16). Queen et al teach that the antibodies can be administered intravenously (see column 23, lines 22-25) and the antibodies can be supplied as kits (see column 24, lines 41-43).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for inhibiting tumor growth comprising administering antibodies that bind VEGFR and EGFR and a chemotherapeutic agent or radiation for therapeutic benefit of human tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a method for inhibiting tumor growth comprising administering antibodies that bind VEGFR and EGFR and further administer a chemotherapeutic agent or radiation for therapeutic benefit of human tumors in view of Rockwell et al and Ciardiello et al and Siemeister et al and Queen et al teach because Rockwell teaches EGFR- and VEGFR-specific antibodies (225 and DC101, respectively) that effectively inhibited A431 tumor cell growth and Ciardiello teach that inhibiting ligand (VEGF) binding to the VEGF receptor or inhibiting ligand (EGF) binding to the EGF receptor results in a mostly cytostatic and reversible growth-inhibitory effect, whereas when ligand binding to both receptors (VEGF and EGF receptors) is inhibited in combination, an almost complete

suppression of tumor growth in all mice was observed and Siemeister et al teach that interfering with VEGF signaling results in the disruption of the sequence of events involved in tumor progression and decreased VEGF expression in tumor cells has been achieved by blocking EGF-stimulated expression of VEGF in A431 tumor cells using an anti-EGFR neutralizing antibody (see page 245). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the EGFR antibody 225 or C225 and the VEGFR antibody DC101 because Ciardiello et al teach that the combined inhibition of ligand binding to EGF and VEGF receptors significantly improved survival and almost completely suppressed tumor growth, whereas inhibition of ligand binding to the EGF receptor or ligand binding to the VEGF receptor results in mostly a cytostatic and reversible growth-inhibitory effect and an anti-EGFR neutralizing antibody decreases EGF-stimulated expression of VEGF in A431 tumor cells, which would interfere with VEGF signaling and disrupt the sequence of events involved in tumor progression according Siemeister, providing additional motivation for the combination of EGFR and VEGFR antibodies. Further, for human therapy one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to produce chimeric and humanized versions of the Rockwell antibodies (225 and DC101) because Queen teaches that chimeric and humanized antibodies are less immunogenic in patients and Rockwell teaches a chimeric version of monoclonal antibody 225 (C225) that binds EGFR with five- to ten-fold higher affinity than monoclonal antibody 225 (see page 317). Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made

to further administer a chemotherapeutic agent or radiation because Rockwell teaches that a synergistic inhibitory affect of A431 tumors was observed with monoclonal antibody 225 and a chemotherapeutic agent when compared with either agent alone and Siemeister teaches that combination treatment with anti-VEGFR monoclonal antibodies and doxorubicin results in a significant enhancement of the efficacy of either agent alone (see page 245, left column) and according to Rockwell "there is mounting preclinical and clinical data that combination therapies may be more efficacious than single agent use" (see page 327). Thus, at the time the claimed invention was made it was known that combinations of substances in cancer treatment enhance the therapeutic efficacy compared with either agent alone. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have produced a method for inhibiting tumor growth comprising administering antibodies that bind VEGFR and EGFR and further administer a chemotherapeutic agent or radiation for therapeutic benefit of human tumors in view of Rockwell et al and Ciardiello et al and Siemeister et al and Queen et al.

Although the claim recites a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Further, it is a well-known convention in the art to place the recited elements in a kit for the advantages of convenience and economy, and methods of detectably labeling antibodies and derivatives thereof also were well known and available to the ordinarily skilled artisan as evidenced in the teachings of Queen et al at columns 19-20 and column 24, lines 41-63.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER